

REMARKS

The present invention concerns methods for identifying new targets for antibacterial agents, thereby allowing greater potential screening assays to identify such agents. As described in the specification, these methods utilize the fact that bacteriophage target particular bacterial proteins with inhibitors encoded by phage genes. Therefore, identifying the target of such a phage-encoded inhibitor identifies a target for antibacterial agents, allowing screening and further development of antibacterial agents. In short, the present invention utilizes the targeting of phage-encoded inhibitors in a discovery method to identify new targets in bacteria.

The claims previously under consideration were cancelled above, and new claims were submitted. Cancellation of the prior claims is not an admission that any of the subject matter of the cancelled claims is unpatentable. Applicant reserves the right to prosecute such claims in this or other appropriate application.

New claim 100 is submitted as a new independent claim specifying that a bacterial protein bound by a bacteriophage-derived protein or fragment that inhibits bacterial growth is a target for antibacterial agents. Dependent claim 101 corresponds to prior claim 37. Dependent claim 102 corresponds to prior claims 61 and 96, but indicates that the fragment is an "active" fragment. Support for the term "active" and definition of the term is provided, for example, at p.11, lines 30-31, p.17, lines 7-10, p.12, lines 25-28, and p.20, lines 25-28. Claims 103 and 104 correspond to prior claims 63, 64, 98, and 99. Support for new claim 105 is provided, for example, at p.12, line 28. Claim 106 corresponds to prior claim 95. Support for claim 107 is provided, for example, at p.12, lines 4-5. Support for new claim 108 is provided, for example, at p.12, lines 3-5. Support for claims 109, 110, and 111 is provided, for example, at p.7, lines 6-7. Support for claims 112 and 113 is provided, for example, at p.11, lines 33-35. Support for new claim 114 is provided, for example, at p.13, lines 22-23 and p.19, lines 10-15. Claim 115 is a new independent claim related to claim 100, except that the method used for identifying interaction between an inhibitory bacteriophage product and a bacterial protein is expressed in means-plus-function for in accordance with 35 U.S.C. § 112, paragraph 6.

Thus, none of the claims submitted present any new matter.

The remarks presented below are referenced to the claim numbers as cited by the Examiner, but, to the extent applicable, are intended to be utilized in connection with the claims submitted above.

Objections to the Specification:

The Examiner objected to the inclusion of embedded hyperlink and/or other form of browser-executable code at particular locations in the Specification.

Applicant has amended the Specification to transform the references to electronically accessible sites so that the site addresses are not in browser-executable form, while still providing sufficient information to identify the site. Applicant submits that, in view of those amendments, the Specification is now in suitable form.

Rejections under 35 U.S.C. § 112 ¶ 1

The Examiner rejected claims 9, 36, 37, 61-64, and 93-99 under 35 U.S.C. § 112, first paragraph, alleging that the Specification does not enable a person skilled in the art to make and/or use the invention commensurate in scope with the claims. Applicant respectfully traverses these rejections.

With respect to claims 9 and 93-95, the Examiner asserted that no limitation exists in the claim to indicate the structure of the bacteriophage inhibitory protein. The Examiner further asserted that specific sequences or structural motifs essential to the practice of the invention, but not included in the claims are not enabled by the disclosure. Further, the Examiner asserted that the inhibitory function of a sequence from bacteriophage 3A ORF corresponding to a cecropin motif has not been demonstrated. Applicant respectfully traverses these rejections.

Preliminarily, it must be recognized that the present invention provides a generally applicable method for identifying targets for antibacterial agents using ORF products from

bacteriophage to identify those targets. Thus, the claims are properly not limited to any particular structural motif or any particular sequence. Indeed, identification of motifs is only utilized in certain embodiments, but is not necessary for numerous other embodiments. Thus, contrary to the Examiner's assertion, identification of specific structural motifs is not required.

In particular, it is irrelevant that an inhibitory function for the phage 3A sequence corresponding to the cecropin motif was not identified. The cecropin motif mentioned by the Examiner is used in a specific illustrative example of a sequence comparison procedure which can be used to find a specific toxic sequence in a bacteriophage amino acid sequence. As mentioned, this procedure represents only one particular application of the invention, not its general practice.

The lack of requirement for motif identification and inhibition associated with the sequence corresponding to specific motifs is clear in the Specification. For example, at page 35, lines 10-12, the Specification indicates that identifying the phage protein or proteins or RNA transcripts that have the ability to inhibit their bacterial hosts can be accomplished by either or both of two non-mutually exclusive methods, only one of which makes use of bioinformatics. In preferred embodiments not utilizing bioinformatics, inhibitor ORFs are identified using a systematic experimental procedure in which each ORF is tested for inhibitory activity by expressing the ORF in host bacteria. See, e.g., page 37, lines 26-34. This approach can be systematically applied to every ORF of the phage, if desired, and does not rely on the absolute identification of candidate ORFs by bioinformatics.

Still focusing on the cecropin motif, the Examiner stated that the sequence alignment data of bacteriophage 77 ORF on page 124, Table 5, does not indicate any motif corresponding to the cecropin motif found in bacteriophage 3A ORF.

However, the absence of an alignment in Table 5 corresponding to the cecropin motif is simply irrelevant to the present claims. Contrary to the Examiner's apparent assumption, Table 5 is not provided to indicate any motif corresponding to the cecropin motif, but rather to

demonstrate the absence of any significant homology of the 6 identified inhibitor ORFs from phage 77, to any sequences described in Swissprot or Genbank. Thus, these ORFs encode novel amino acid sequences able to inhibit bacterial growth. This further demonstrates that specific motifs do not need to be known or identified to practice the present invention.

The Examiner also asserted that it would require undue experimentation for a person having ordinary skill in the art to be able to practice the claimed invention because no guidance has been provided such that a person having ordinary skill in the art would know the structure with reference to the binding site of the bacteriophage inhibitory protein, and further stated that there is no description given for a binding assay wherein it demonstrates the binding of a bacteriophage inhibitory protein to a bacterial target protein.

Quite to the opposite of requiring undue experimentation, a person of ordinary skill in the art would readily be able to identify specific sequences corresponding to bacteriophage inhibitory ORFs and the encoded products using the description provided by the Specification. Such a person would also readily be able to carry out the inhibition tests as described. While such procedures are routine, references which provide further guidance for the identification of phage-derived inhibitor proteins and their amino acid sequences are also provided in the application. For example, these include:

- 1) for standard methodologies employed in the art for phage and bacterial culture, bacterial transformation and assay for bacterial toxicity: See, e.g., Specification page 31, lines 28-36, Maloy, S.R., Stewart, V.J., and Taylor, R.K. Genetic Analysis of Pathogenic Bacteria (1996) Cold Spring Harbor Laboratory Press, or Maniatis, T. et al. (1989) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor University Press, Cold Spring, N.Y.; or Ausubel, F.M. et al. (1994) Current Protocols in Molecular Biology. John Wiley & Sons, Secaucus, N.J.
- 2) for standard procedures for molecular biology including, DNA sequencing, ORF cloning and induction of ORF expression: See, e.g., Specification p.38, line 36 to p.39, line 3, Current Protocols in Protein Science, John Wiley & Sons, Secaucus, N.J.,

and Maniatis, T. et al. (1989) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor University Press, Cold Spring, N.Y.

Indeed, using the procedure described in the present application, 6 proteins derived from phage 77 were identified which inhibit bacterial growth in solid and liquid assays. Identification of these inhibitor ORFs is described in detail in the parent application (US Application 09/407,804), which is incorporated by reference in the present specification, and did not require undue experimentation. Instead, the identification involved routine application of the approach described in the present application.

Further, utilizing the bacteriophage products that inhibit bacteria, one of ordinary skill in the art can readily utilize those products to identify bacterial proteins to which they bind or otherwise interact. A number of techniques useful for such identification are described in the Specification.

For example, in addition to conventional direct binding assay, which one of ordinary skill in the art can readily construct for particular ORF products, the specification also provides guidance for bacterial target protein identification based on protein:protein interaction using identified inhibitory proteins from bacteriophage. Inhibitory proteins or fragment therefrom can be purified by standard procedures of protein purification, and used in affinity chromatography following laboratory routine procedures as referred in the specification. See, e.g., p. 38, line 36 to p.39, line 4, referencing Current Protocols in Protein Science, John Wiley & Sons, Secaucus, N.J., and Maniatis, T. et al. (1989) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor University Press, Cold Spring, N.Y. Likewise, on p.44-45, a description and a reference to a scientific paper is provided for a technique using affinity chromatography. As described, this technique was used to identify *E. coli* proteins that bind to bacteriophage lambda proteins. (Sopta, M., Carthew, R.W., and Greenblatt, J. (1985) J. Biol. Chem. 260, 10353-10369).

Indeed, as described in PCT Publication WO 0146383, "Composition and methods involving an essential *Staphylococcus aureus* gene and its encoded protein", the bacterial target of one of the inhibitory ORFs of phage 77 was identified using the procedure described in the

present application. Carrying out the procedure to identify the bacterial target did not require undue experimentation.

The Examiner also alleged that the nature of the invention relates to the generation of any sequence encoding bacteriophage inhibitor protein but no indication has been made as to what activity the encoded protein must have.

Quite to the contrary, the “activity” of the encoded phage ORF product is clearly described in the specification as an ability to inhibit bacterial growth using standard laboratory procedures. For example, on page 35, lines 9-10, the Specification refers to “identifying the phage protein or proteins or RNA transcripts that have the ability to inhibit their bacterial hosts.” (Emphasis added.)

Further, Applicant respectfully submits that the Examiner’s reference to knowing the structure with reference to the binding site of the bacteriophage inhibitory protein is irrelevant to the present claims. As described throughout the Specification, the identification of targets in bacteria can be carried out without identification of binding sites or motifs or other sub-structure of the bacteriophage ORF product used for the identification. While the Specification also describes embodiments in which such information can be utilized, it is not necessary to the practice of the present claimed invention. Furthermore, techniques for identifying such binding sites are known in the art, and can be utilized for those embodiments specifying identification or knowledge of particular binding sites. Application of such common techniques does not involve undue experimentation.

With respect to claim 36, the Examiner stated that the claim is directed to a method wherein the binding is determined using affinity chromatography on a solid matrix. The Examiner alleged that the Specification fails to provide a specific description for the condition of the assay for the binding of bacteriophage inhibitory protein to the bacterial target protein.

Applicant believes that the Examiner intended to refer to claim 37, which specifies “affinity chromatography on a solid matrix.” Therefore, the following comments refer to claim

37, rather than claim 36. If this is incorrect, Applicant respectfully requests that the Examiner clarify the rejection of claim 36.

One of ordinary skill in the art of conducting affinity chromatography readily understands that the specific conditions for carrying out affinity chromatography will depend on the particular binding molecules involved. Nonetheless, the conditions of the assay for the binding of bacteriophage inhibitory protein follow the standard procedures as described in the specification. Inhibitory ORFs or a fragment therefrom can be purified by standard procedures of protein purification and used in affinity chromatography following routine laboratory procedures.

In addition, standard methodologies for expressing proteins from constructs, and isolating and manipulating those proteins, for example in cross-linking and affinity chromatography studies, may be found in various commonly available and known laboratory manuals. See, e.g., Current Protocols in Protein Science, John Wiley & Sons, Secaucus, N.J., and Maniatis, T. et al. (1989) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor University Press, Cold Spring, N.Y. See, e.g., the Specification on p.38, line 36 to p.38, line 3.

Further direction is provided (see, e.g., Specification p.44, beginning at line 5), which refers to an approach is based on identifying protein:protein interactions between the phage ORF product and bacterial *S. aureus*, e.g., proteins using a biochemical approach based, for example, on affinity chromatography. This approach has been used, for example, to identify interactions between lambda phage proteins and proteins from their *E. coli* host (Sopta, M., Carthew, R.W., and Greenblatt, J. (1985) *J. Biol. Chem.* 260, 10353-10369) (Specification, p.44, lines 8-10.).

Thus, claim 37 provides the specificity appropriate to the proper scope of the claim, because is not possible to specify specific conditions that would be applicable to the different types of phage-derived proteins that inhibit the host bacteria. However, determination of such conditions for affinity chromatograph would not involve undue experimentation for one of ordinary skill in the art, but instead would involve only routine testing to select the conditions. Therefore, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

The Examiner indicated that claims 61-64 and 97-99 are directed to a method, wherein, the bacterial target protein binds to a fragment of bacteriophage inhibitory protein, and further stated that no biological activities were attributed to the recited protein fragments and the structural information was limited. The Examiner further alleged that there is no disclosure about the binding activities of claimed fragments. The Examiner therefore asserted that undue experimentation would be required to make and use the claimed protein fragments.

Contrary to the Examiner's assertions, the specification provides a definition of fragment and, as mentioned, specified that in preferred embodiments, the fragments of the ORF to be used are "active" i.e. they harbor bacteria-inhibiting function. The active fragment can be used to identify a bacterial target protein in a binding assay. Support for fragments and associated activity was pointed out above at p.11, lines 30-31, p.17, lines 7-10, p.12, lines 25-28, and p.20, lines 25-28, in connection with claim 102.

In addition, construction and testing for identification of active fragments of a protein that retains a particular activity is routine in view of the expression assay for inhibition described in the Specification. Techniques for constructing fragments are very well known, and utilize common techniques, for example as provided in common laboratory manuals such as those cited at p.39, lines 1-3. Thus, no undue experimentation would be involved, only routine laboratory procedures.

The Examiner also objected to the use of certain terms. While Applicant does not agree with the Examiners assertions concerning those terms, those terms are not in the present claims. Therefore, the Examiner's comments on those terms are inapplicable to the present claims.

The Examiner also stated that the Specification fails to describe or demonstrate the invention as claimed.

While Applicant did not describe the specific identification of a bacterial target in the present Specification, Applicant has amply described how to carry out such identification. Further, target identification according to the present claims has, in fact, been performed. As indicated above, such target identification was described in PCT Publication WO 0146383. The target identification described in that related International Application demonstrates that the methods of the present claims are effective to identify targets in bacteria, and that such identification does not involve undue experimentation.

In summary, the Examiner put forth numerous assertions in support of the allegation that undue experimentation would be involved to practice the claimed invention. However, as indicated above, the Specification provides ample description to enable one of ordinary skill in the art to carry out the claimed methods with only routine procedures and testing of conditions and constructs. As the Federal Circuit has consistently held, the Specification is not required to provide a cookbook. Indeed, routine information is preferably excluded. Further, the Court has consistently held that substantial experimentation is allowable. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

In this case and in accordance with the remarks above and the factors provided in *In re Wands*, Applicant submits that the claimed methods involve only routine procedures and testing that one of ordinary skill in the art can readily carry out without undue experimentation. Thus, Applicant respectfully requests that the Examiner reconsider and withdraw the rejections for alleged lack of enablement with respect to the pending claims.

Rejections under 35 U.S.C. § 112, ¶ 2

The Examiner rejected claims 9, 36, 37, and 93-96 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. The Examiner alleged that the term “uncharacterized”

rendered claim 9 indefinite, and that the terms “untargeted” and “potential target” rendered claim 93 indefinite. The Examiner further alleged that claims 61 and 96 are indefinite as to fragment size. Applicant respectfully traverses these rejections.

While Applicant does not agree with the Examiner that the cited terms render the claims indefinite, Applicant submitted new claims that do not contain the terms noted by the Examiner. Therefore, Applicant respectfully requests that the Examiner withdraw this rejection.

Further, with respect to fragment size, for amino acid sequences, Applicant defined “fragment” in the Specification as containing at least 5 linked amino acid residues. See, Specification, p.12, lines 25-31. Thus, contrary to the Examiner’s assertion on p.7 of the Action, a “fragment” cannot be a single amino acid, but must be at least 5 contiguous linked amino acid residues.

In view of the definition of “fragment” provided in the Specification, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that the claims are allowable and request a notice to that effect.

Should a telephonic discussion appear helpful in furthering prosecution of the present application, the Examiner is encouraged to contact the undersigned at the telephone number listed below.

No fee is believed due in connection with this communication. However, if any fee is due, kindly charge the appropriate amount to Deposit Account 50-0872.

Date 22 October 2001

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Respectfully submitted,

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Appendix 1 – Clean copies of replacement paragraphs

(Replacement paragraph to replace the paragraph beginning at p.35, line 9)

The fourth step entails identifying the phage protein or proteins or RNA transcripts that have the ability to inhibit their bacterial hosts. This can be accomplished, for example, by either or both of two non-mutually exclusive methods. The first method makes use of bioinformatics. Over the past few years, a large amount of nucleotide sequence information and corresponding translated products have become available through large genome sequencing projects for a variety of organisms including mammals, insects, plants, unicellular eukaryotes (yeast and fungi), as well as several bacterial genomes such as *E. coli*, *Mycobacterium tuberculosis*, *Bacillus subtilis*, *Staphylococcus aureus* and many others. Such sequences have been deposited in public databases (for example, non-redundant sequence database at GenBank and SwissProt protein sequence database) (on the World Wide Web, with the remainder of the address being ncbi.nlm.nih.gov) and can be freely accessed to compare any specific query sequence to those present in such databases. For example, GenBank contains over 1.6 billion nucleotides corresponding to 2.3 million sequence records. Several computer programs and servers (e.g., TBLASTN) have been created to allow the rapid identification of homology between any given sequence from one organism to that of another present in such databases, and such programs are public and available free of charge.

(Replacement paragraph to replace the paragraph beginning at p.63, line 12 and extending to line 31)

An implementation of the publicly available program SEQUIN, available for download at an ftp site (the remainder of the address is ncbi.nlm.nih.gov/sequin/), was used on phage genome sequence to identify all putative ORFs larger than 33 codons. A listing of such ORFs for *S. aureus* phage 77 is shown in Fig. 2, with predicted amino acid sequences shown in Fig. 3. Listings of ORFs for phage 3A and 96 are provided in Figs. 7 and 9 respectively. A variety of other ORF identification could be used as alternatives and are known to those skilled in the art.

Sequence homology searches for each ORF are then carried out using a standard implementation of blast programs. Downloaded public databases used for sequence analysis include:

non-redundant GenBank (available at an ftp site, with the remainder of the address being [ncbi.nlm.nih.gov/blast/db/nr.Z](ftp://ncbi.nlm.nih.gov/blast/db/nr.Z)),

Swissprot (available at an ftp site, with the remainder of the address being [ncbi.nlm.nih.gov/blast/db/swissprot.Z](ftp://ncbi.nlm.nih.gov/blast/db/swissprot.Z));

Vector (available at an ftp site, with the remainder of the address being [ncbi.nlm.nih.gov/blast/db/vector.Z](ftp://ncbi.nlm.nih.gov/blast/db/vector.Z));

pdbs databases (available at an ftp site, with the remainder of the address being [ncbi.nlm.nih.gov/blast/db/pdbaa.Z](ftp://ncbi.nlm.nih.gov/blast/db/pdbaa.Z));

staphylococcus aureus NCTC 8325 (available at an ftp site, with the remainder of the address being [genome.ou.edu/pub/staph/staph-1k.fa](ftp://genome.ou.edu/pub/staph/staph-1k.fa));

streptococcus pyogenes (available at an ftp site, with the remainder of the address being [genome.ou.edu/pub/strep/strep-1k.fa](ftp://genome.ou.edu/pub/strep/strep-1k.fa));

streptococcus pneumoniae available at an ftp site, with the remainder of the address being [tigr.org/pub/data/s_pneumoniae/gsp.contigs.112197.Z](ftp://tigr.org/pub/data/s_pneumoniae/gsp.contigs.112197.Z));

mycobacterium tuberculosis CSU#9 (available at an ftp site, with the remainder of the address being [tigr.org/pub/data/m_tuberculosis/TB_091097.Z](ftp://tigr.org/pub/data/m_tuberculosis/TB_091097.Z)); and

pseudomonas aeruginosa (available on the World Wide Web, with the remainder of the address being genome.washington.edu/pseudo/data.html).

Appendix 2 – Marked-up copies of replacement paragraphs

(Paragraph beginning at p.35, line 9)

The fourth step entails identifying the phage protein or proteins or RNA transcripts that have the ability to inhibit their bacterial hosts. This can be accomplished, for example, by either or both of two non-mutually exclusive methods. The first method makes use of bioinformatics. Over the past few years, a large amount of nucleotide sequence information and corresponding translated products ha(on the World Wide Web, with the remainder of the address being ve become available through large genome sequencing projects for a variety of organisms including mammals, insects, plants, unicellular eukaryotes (yeast and fungi), as well as several bacterial genomes such as *E. coli*, *Mycobacterium tuberculosis*, *Bacillus subtilis*, *Staphylococcus aureus* and many others. Such sequences have been deposited in public databases (for example, non-redundant sequence database at GenBank and SwissProt protein sequence database) (on the World Wide Web, with the remainder of the address being [ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov)) [<http://www.ncbi.nlm.nih.gov>]] and can be freely accessed to compare any specific query sequence to those present in such databases. For example, GenBank contains over 1.6 billion nucleotides corresponding to 2.3 million sequence records. Several computer programs and servers (*e.g.*, TBLASTN) have been created to allow the rapid identification of homology between any given sequence from one organism to that of another present in such databases, and such programs are public and available free of charge.

(paragraph beginning on p.63, line 12 and extending to line 31)

An implementation of the publicly available program SEQUIN, available for download at an ftp site (the remainder of the address is [negi.nlm.nih.gov/sequin/](ftp://negi.nlm.nih.gov/sequin/)) [<ftp://negi.nlm.nih.gov/sequin/>], was used on phage genome sequence to identify all putative ORFs larger than 33 codons. A listing of such ORFs for *S. aureus* phage 77 is shown in Fig. 2, with predicted amino acid sequences shown in Fig. 3. Listings of ORFs for phage 3A and 96 are provided in Figs. 7 and 9 respectively. A variety of other ORF identification could be used as

alternatives and are known to those skilled in the art. Sequence homology searches for each ORF are then carried out using a standard implementation of blast programs. Downloaded public databases used for sequence analysis include:

non-redundant GenBank (available at an ftp site, with the remainder of the address being [ncbi.nlm.nih.gov/blast/db/nr.Z](ftp://ncbi.nlm.nih.gov/blast/db/nr.Z)) [(ftp://ncbi.nlm.nih.gov/blast/db/nr.Z)],

Swissprot (available at an ftp site, with the remainder of the address being [ncbi.nlm.nih.gov/blast/db/swissprot.Z](ftp://ncbi.nlm.nih.gov/blast/db/swissprot.Z)) [(ftp://ncbi.nlm.nih.gov/blast/db/swissprot.Z)];

Vector (available at an ftp site, with the remainder of the address being [ncbi.nlm.nih.gov/blast/db/vector.Z](ftp://ncbi.nlm.nih.gov/blast/db/vector.Z)) [(ftp://ncbi.nlm.nih.gov/blast/db/vector.Z)];

pdbaa databases (available at an ftp site, with the remainder of the address being [ncbi.nlm.nih.gov/blast/db/pdbaa.Z](ftp://ncbi.nlm.nih.gov/blast/db/pdbaa.Z)) [(ftp://ncbi.nlm.nih.gov/blast/db/pdbaa.Z)];

staphylococcus aureus NCTC 8325 (available at an ftp site, with the remainder of the address being [genome.ou.edu/pub/staph/staph-1k.fa](ftp://ftp.genome.ou.edu/pub/staph/staph-1k.fa)) [(ftp://ftp.genome.ou.edu/pub/staph/staph-1k.fa)];

streptococcus pyogenes (available at an ftp site, with the remainder of the address being [genome.ou.edu/pub/strep/strep-1k.fa](ftp://ftp.genome.ou.edu/pub/strep/strep-1k.fa)) [(ftp://ftp.genome.ou.edu/pub/strep/strep-1k.fa)];

streptococcus pneumoniae (available at an ftp site, with the remainder of the address being [tigr.org/pub/data/s_pneumoniae/gsp.contigs.112197.Z](ftp://ftp.tigr.org/pub/data/s_pneumoniae/gsp.contigs.112197.Z))

[(ftp://ftp.tigr.org/pub/data/s_pneumoniae/gsp.contigs.112197.Z)];

mycobacterium tuberculosis CSU#9 (available at an ftp site, with the remainder of the address being [tigr.org/pub/data/m_tuberculosis/TB_091097.Z](ftp://ftp.tigr.org/pub/data/m_tuberculosis/TB_091097.Z))

[(ftp://ftp.tigr.org/pub/data/m_tuberculosis/TB_091097.Z)]; and

pseudomonas aeruginosa (available on the World Wide Web, with the remainder of the address being [genome.washington.edu/pseudo/data.html](http://www.genome.washington.edu/pseudo/data.html))

[(<http://www.genome.washington.edu/pseudo/data.html>)].